UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,437	03/20/2006	Walter Gumbrecht	32860-000900/US	6672

30596 7590 03/17/2009

HARNESS, DICKEY & PIERCE, P.L.C.
P.O.BOX 8910
RESTON, VA 20195

EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
03/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,437	GUMBRECHT ET AL.	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-21* is/are pending in the application.

4a) Of the above claim(s) *11-15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,17,18, 20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed December 17, 2008 is acknowledged. Claims 1, 5, 7-10, 17 and 18 (currently amended), claims 3, 4 and 6 (previously presented) and claims 20 and 21 (newly added) will be examined on the merits. Claims 11-15 and 19 were previously withdrawn and claims 2 and 16 were previously canceled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim was amended to recite the phrase "wherein subjecting the array to the thermocycling process includes elongating a counter strand of the DNA fragment within the reaction layer with the aid of a primer which specifically hybridizes with one of the target sequences immobilized in the analyte solution". It is unclear how target sequences can be immobilized in the analyte solution, since immobilization would require that the target sequences are no longer in solution.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 3, 4, 7, 8, 17, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent Pub. No. 2002/0155586) in view of Frechet et al. (U.S. Patent Pub. No. 2004/0101442) and further in view of Hodko et al. (Proc. SPIE (2001) 4265:65-74, cited on IDS, 6/20/2005).

With regard to claims 1 and 21, Cheng teaches a method for PCR amplification and detection of nucleotide sequences (for overview, see Abstract), comprising:

using a reaction layer for binding of probe molecules and an array of a plurality of microspots forming analytical positions (a flow cell comprises an electronically addressable microarray, paragraph 60, lines 1-6 and Figure 5; the system may include a permeation layer overlaying the electrodes, and the probes may be coupled to the permeation layer, paragraph 24, lines 1-3 and claims 5 and 6), said microspots including as probe molecule at least one immobilized oligonucleotide which is

hybridizable with a target sequence to be identified of a DNA fragment (nucleic acid probes are attached to the microarray for the purpose of detection of nucleic acids of interest such as amplification products, paragraph 34, lines 1-8 and paragraph 91, lines 1-8);

applying an analyte solution including PCR reagents and a plurality of target sequences to the microspots such that the analyte solution completely covers the array (the flow cell provides a compartment for containing biological sample materials and buffers to be layered on top of the microchip, including those needed for PCR amplification, paragraph 55, lines 5-15 and paragraph 61, lines 4-6);

subjecting the array to a thermocycling process to amplify the target sequences (heating element, part 12 of Figure 5, can be used for temperature cycling for nucleic acid PCR amplification within the flow cell, paragraph 56, lines 8-12 and paragraph 77, lines 7-11); and

detecting hybridization events on the probe molecules immobilized at one of the analytical positions electrochemically with the aid of a microelectrode arrangement (analyte detection may be accomplished through electrochemical detection, paragraph 55, lines 15-19; target species such as amplified products are electronically addressed to specified capture pads or coated electrodes for capture by anchored capture oligonucleotides, paragraph 92, lines 1-5, for detection using fluorophore-labeled reporter probes and a CCD-based optical imaging system, lines 12-16 or through a direct electrochemical voltammetric detection system, paragraph 97, lines 7-11).

With regard to claims 3 and 4, Cheng teaches a method wherein a reaction layer, such as a hyrdogel based on acrylamide and having coupling groups for covalent binding of probe molecules is used (microchips are coated with a permeation layer such as a hydrogel of acrylamide which can be coupled with probes, paragraph 24, lines 1-3, paragraph 60, lines 14-21 and paragraph 92, lines 1-10).

With regard to claims 7, 8 and 17 Cheng teaches a method wherein the analyte solution includes an external primer pair that hybridizes with a target DNA outside the target sequences and also includes a plurality of DNA fragments having a different target sequence (a concentrated amplification reagent is introduced into the flow cell and contains primer pairs flanking the spa Q and inv A gene target regions such that any variations with the genes will be amplified, paragraph 79, lines 6-15 and paragraphs 80-83).

With regard to claim 20, Cheng teaches a method wherein an electronically addressable microchip containing a 1 inch square grid array has at least 100 individually addressable microelectrodes such that a diaelectric force pattern may be generated across the microchip electronic grid (paragraph 60, lines 1-6 and paragraph 69, lines 1-6)

Cheng does not teach a method for PCR amplification and detection of nucleotide sequences using a hydrophilic reaction layer having coupling groups for covalent binding of probe molecules, including a cross-linkable hydrogel based on acrylamide with either maleic anhydride or glycidyl (meth)acrylate as coupling groups.

Cheng also does not teach a method wherein detected nucleotide sequences alter impedance of the microelectrode arrangement. Cheng also does not teach a method wherein each electrode of the microelectrode arrangement has a width of 1 μm to 10 μm and a height of 100 nm to 500 nm, and wherein the reaction layer has a thickness of 5 μm to 10 μm.

Frechet teaches methods of grafting polymer monolith surfaces for microfluidic devices such as a "lab on a chip" that includes attachment of polymer chains having functional groups such as hydrophilic or reactive groups comprising acrylamide that bears functional groups including glycidyl methacrylate (paragraph 6, lines 1-17, paragraph 27, lines 1-10, paragraph 28, lines 1-3 and paragraph 29, lines 1-7). Frechet also teaches a method wherein the channels containing the polymer monolith surfaces are 10-200 μm deep (paragraph 20, lines 1-3).

Hodko teaches a method for detection of pathogens based on electrochemical detection of PCR amplified molecules specific for the pathogen wherein the detection method is based on electrochemical AC impedance analysis using redox probes capable of intercalating into double-stranded DNA products in contact with platinum electrodes (p. 66, lines 16-19 and p. 68, lines 1-12).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Cheng for making and

using an integrated system such as a chip for amplification and detection of nucleic acid targets directly on the chip device with the methods of Frechet for making similar lab-on-a-chip devices that can contain any of a variety polymers grafted to the surface that have functional groups attached that would be useful for covalent attachment of the oligonucleotide capture probes taught by Cheng, and also with the methods of Hodko, since this reference provides an alternative method for detection of PCR products in a microfluidic or chip device. Thus, an ordinary practitioner would have been motivated to combine the methods of Cheng, Frechet and Hodko since the substrates containing capture probes taught by Cheng, which can be formed in the permeation layer (Cheng, paragraph 24, lines 1-3), are highly suitable for being formed above the thermoplastic polymer surfaces taught by Frechet used for making microfluidic devices. Frechet teaches the formation of first and second monomers which are used to form porous layers within a microfluidic channel by a photopolymerizing technique, followed by addition of a third layer comprising the polymer with functional groups (paragraph 27, lines 4-10, paragraph 31, lines 1-17 and paragraph 32, lines 1-3), since this layer can contain the capture probes immobilized in the permeation reaction layer needed for detection by hybridization of amplified products to the capture probes. The permeation layer is useful for protecting the biomolecules of interest from the electrochemistry occurring at the electrode surface (Cheng, paragraph 60, lines 14-21) and would be further protected by the additional layer or layers taught by Frechet that are attached closest to the chip surface under the permeation layer. Furthermore, the formation of double-stranded products at the electrode surface can be detected using the

electrochemical AC impedance method of Hodko since this method "is easily adapted to a microfluidic environment" (Hodko, p. 66, lines 16-18), providing direct detection of PCR amplicons within a thin microfulidic chamber with no need for modifying the electrodes (Hodko, p. 66, lines 30-32 and p. 72, lines 24-26), without interference from PCR reagents present in the sample (Hodko, p. 72, line 26).

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made optimize the size of the microelectrodes with the microelectrode arrangement based on the desired size and density of the electronic grid, as well as the depth or thickness of the reaction layer over the grid. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that, based on the size and density of grid arrays as taught by Cheng (paragraph 60, lines 1-6 and paragraph 69, lines 1-6) and the size and depth of channels used as sites for forming polymer monolith surfaces as taught by Frechet (paragraph 20, lines 1-3), the exact dimensions of the microelectrodes and reaction layers could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific dimensions of the microelectrodes and reaction layers was other than routine, that the methods or products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Thus, an ordinary practitioner would have recognized that the dimensions of the microelectrodes and reaction layers could be adjusted to maximize the desired results.

7. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent Pub. No. 2002/0155586) in view of Frechet et al. (U.S. Patent Pub. No. 2004/0101442) and further in view of Hodko et al. (Proc. SPIE (2001) 4265:65-74, cited on IDS, 6/20/2005) as applied to claims 1, 3, 4, 7, 8, 17, 20 and 21 above, and further in view of Ghodsian, B. (U.S. Patent Pub. No. 2002/0115293).

Cheng, Frechet and Hodko together teach the limitations of claims 1, 3, 4, 7, 8, 17, 20 and 21, as discussed above.

With regard to claim 5, Cheng also teaches a method wherein a biochip including a substrate layer and an insulating layer connected therewith is used, wherein the electrode arrangement and the reaction layer are carried on a side of the insulating layer, which faces away from the substrate layer (an electronically addressable microarray is mounted onto a substrate, to the back of which is attached a ceramic heater, while a protective permeation layer coats the microchips, facing away from the

substrate, and protects the biomaterials from being directly exposed to the electrodes in the microchips, paragraph 60, lines 1-21 and Figure 5).

However, neither Cheng nor Frechet nor Hodko teach a method using a biochip comprising a substrate comprising a semiconductor layer wherein the layer is a silicon layer.

Ghodsian teaches the making of and use of devices for DNA sequencing including lab-on-a-chip devices comprising a substrate that are semiconductors composed of silicon that are useful for integration of active circuits (paragraph 201, lines 1-11).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Cheng, Frechet and Hodko for making and using an integrated system such as a chip for amplification and detection of nucleic acid targets directly on the chip device with the methods of Ghodsian for making and using similar lab-on-a-chip devices for DNA sequencing since both systems use devices comprising substrates with integrated electronic circuitry for performing or controlling biological reactions, including DNA synthetic processes such as PCR and DNA sequencing. Thus, an ordinary practitioner would have been motivated to combine the methods of Cheng, Frechet, Hodko and Ghodsian since the substrates taught by Cheng and Frechet are highly suitable for being formed of the semiconductor silicon as taught by Ghodsian since this material is ideal for

micromachining and the integration of electronic circuits (Ghodsian, paragraph 201, lines 1-7) needed for detection of hybridization of amplified products to capture probes immobilized in a reaction layer, which can be attached to the silicon substrate in the devices of Cheng and Frechet to form the bottom layer of the flow chamber (Cheng, paragraph 61, lines 1-6). Finally, Hodko provides an electrochemical impedance method for detection of PCR amplification products that is easily adapted to a microfluidic environment (Hodko, p. 66, lines 16-18).

8. Claims 9, 10 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent Pub. No. 2002/0155586) in view of Frechet et al. (U.S. Patent Pub. No. 2004/0101442) and further in view of Hodko et al. (Proc. SPIE (2001) 4265:65-74, cited on IDS, 6/20/2005) as applied to claims 1, 3, 4, 7, 8, 17, 20 and 21 above, and further in view of Strizhkov et al. (BioTechniques (2000) 29:844-846, 848, 850-852, 854, 856-857).

Cheng, Frechet and Hodko together teach the limitations of claims 1, 3, 4, 7, 8, 17, 20 and 21, as discussed above.

However, neither Cheng nor Frechet nor Hodko teaches a method wherein a target is amplified using both an internal primer or primer pair immobilized within a reaction layer and an external primer and wherein the products are further amplified using internal primers immobilized within a reaction layer.

Strizhkov teaches a method of PCR amplification on a microarray using solution-based forward and reverse primers as well as internal primers immobilized inside a gel pad (p. 848, column 1, line 46 to column 2, line 17).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Cheng, Frechet and Hodko for making and using an integrated system such as a chip for amplification and detection of nucleic acid targets directly on the hyrdogel layer of the chip device with the methods of Strizhkov, who also teaches methods of PCR amplification on a microarray using primers both in solution and immobilized on a surface such as a gel pad. Thus, an ordinary practitioner would have been motivated to combine the methods of Cheng, Frechet, Hodko and Strizhkov since the methods of PCR amplification taught by Strizhkov using both solution-phase outer primers and solid-phase inner primers can be readily adapted to the microarray methods of Cheng wherein amplification can first take place, as it normally does, in the chamber of the flow cell using solution-based outer primers, followed by capture of the amplification products by immobilized capture probes that also serve as inner forward primers to initiate a second round of amplification on the surface of the hydrogel layer. This modified system is similar to nested primer amplification and is useful for increasing the specificity of the procedure (Strizhkov, p. 848, column 2, lines 12-16). Finally, Hodko provides an electrochemical impedance method for detection of PCR amplification products that is easily adapted to a microfluidic environment (Hodko, p. 66, lines 16-18).

Response to Arguments

9. Applicant's additional arguments with respect to the previous rejections of record have been noted, but are moot in view of the rejection of the claims based on new grounds.

Summary

10. Claims 1, 3-10, 17, 18, 20 and 21 are rejected. No claims are allowable.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637